Original Article

Clinical characteristics of males with systemic lupus erythematosus (SLE) in an inception cohort of patients in Ghana

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SUMMARY

Background: Systemic Lupus Erythematosus (SLE) is said to be rare in Sub-Saharan Africa and even rarer in males worldwide. SLE is mostly considered a disease of women, though men may also be affected, and this may lead to a delay in diagnosis in men. The result is a greater burden of inflammation and subsequent organ damage over time.
Method: Data from the medical records of 13 male patients diagnosed with SLE at the Rheumatology Clinic of Korle-Bu Teaching Hospital between January 2014 and January 2017 was retrospectively analyzed.
Results: A total of 13 male patients out of a total of 134 SLE patients were included in our analysis. The mean age was 30.62 ± SD 8.47 years (range of 17 to 46 years). All of them (100%) presented with constitutional features. The most common ACR criteria observed was 61.5 % rash, 54.5 % oral ulcers, 92.3% arthritis, 61.5 % serositis and 38.5% renal involvement, 46.2 % CNS involvement. Looking at their serological profile, 91.7 % had a positive antinuclear antibody (ANA). 33.3 % had positive anti-dsDNA and 58.3 % extractable nuclear antigens. The mean duration from onset of symptoms to diagnosis was 21.31 months. Five patients were diagnosed with lupus nephritis, all at the time of diagnosis. There were no mortalities.
Conclusion: Male SLE patients in Ghana are comparable to other populations, with arthritis and constitutional features being predominant early features and lupus nephritis being the main early indicator of organ damage. This should warrant aggressive management in male patients.

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INTRODUCTION

SLE is a clinically heterogeneous autoimmune disease of unknown etiology. It is characterized serologically by autoantibodies targeting self-proteins. Organs and cells of affected individuals undergo damage mediated by tissue-binding autoantibodies and immune complexes.

The onset and severity of symptoms appears to be influenced by environmental factors (such as sunlight, drugs and chemicals, and infectious agents), coupled with a strong underlying genetic susceptibility to this complex disease.[1] SLE is said to be rare in Sub-Saharan Africa and even rarer in males worldwide.

The incidence of SLE is markedly increased in females of child-bearing age with a male to female ratio of 8-15:1, suggesting a hormonal influences in the cause.[2] Further evidence for hormonal influence comes from the fact that the ratio of female to male cases is much lower in prepubertal children and after menopause, although a female predominance remains.[3] Reported pre-pubertal and post-menopausal ratios are much lower at 2–6:1 and 3–8:1 respectively.[4]

Factors accounting for female predominance

Potential causes of the female predilection for SLE included the effects of estrogen and its hydroxylation, decreased androgen levels, hyperprolactinemia and differences in gonadotropin-releasing hormone (GnRH) signaling.[5]

Sex hormones have been shown to interact with the immune system, including the B cell and T cell compartment, dendritic cells and cytokine networks. It is thought that female sex hormones cause enhanced autoimmune reactivity and contribute to the immunological disconcertion that results in SLE.[6] The female hormonal influences include supporting the survival of autoreactive B cells and modifying their maturation toward a marginal zone phenotype, while male hormones produce the opposite effects. [7]

A publication by Cattalani et al., outlining differences between sexes in paediatric patients revealed sex dimorphism to be less evident in childhood autoimmune disease possibly on account of minor differences in hormonal environment between males and females.[8] Krassaelt and Baerwald in a review highlights that female sex hormones like estradiol not only increase risk of SLE but also influence the course of the disease.[9] The use of exogenous hormones has been associated with lupus onset and flares, suggesting a role for hormonal factors in the pathogenesis of the disease.[10]

Interestingly, in men, SLE is suggested to be more common in those with Klinefelter Syndrome (ie, genotype XXY), further supporting a hormonal hypothesis.[11] In fact, a study by Dillon et al found that men with SLE and Klinefelter syndrome had a more severe course of SLE than women, but they had a less severe course than other men.[12] A study done on the profile of sex hormones in male patients with systemic lupus erythematosus showed no significant differences in serum Testosterone (T), Estrogen (E2), Prolactin(PRL) levels and E2/T ratio between male SLE patients and controls. However, patients with SLE had significantly higher levels of gonadotrophins.[13]

Differences in Clinical Presentation of Male SLE

The greater awareness of SLE as a potential diagnosis in females, may lead to a greater delay in diagnosis in men presenting with similar symptoms. The consequence would be a greater burden of inflammation and subsequent damage over time. Alternatively, if men displayed an atypical phenotype at presentation, a delay in diagnosis, and thus treatment, might result .[14] In a study done by Tan et al,[15] men were more likely than women to have disability.

Men were more likely to be diagnosed at an older age and to have a lower education level. Men were more likely than women to have experienced end organ damage including neuropsychiatric, renal, cardiovascular, peripheral vascular disease, and myocardial infarction, and to have died.

Earlier studies on male SLE have suggested a higher mortality due to kidney and hematological disease and for male SLE patients to be more likely to be of African descent.[16] In general, differences between males and females are numerous and more striking in Caucasians, especially with respect to lupus nephritis, abnormal serologies and thrombosis.[15]

However, a full explanation for why the disease is so uncommon in men remains elusive and which patterns maybe representative for males with SLE. We sought to examine the clinical pattern in male SLE patients in the Ghana Lupus Cohort in order to improve the body of knowledge in this rare group.

METHODS

Study population

We retrospectively assessed the medical records of 13 male patients diagnosed with Systemic Lupus erythematosus (SLE) who were attendant at the rheumatology clinic of Korle-Bu Teaching Hospital (KBTH), Male patients who were diagnosed to have SLE using clinical and laboratory criteria in keeping the American College of Rheumatology (ACR) criteria[17] and followed up in our cohort, had their data collected retrospectively. There was a total of 134 SLE patients diagnosed between January 2014 and January 2017.

Patients were only included if they had at least one follow-up visit. Patients with only discoid lupus were excluded. The patients had all been under the care of the Rheumatologists at the KBTH and were subject to usual care and or more frequent reviews as dictated by their condition.

Information recorded at cohort entry (and updated at each visit) consists of basic demographic characteristics (date of birth, age at SLE onset, ethnicity, sex, socioeconomic status, and years of education, occupation, presenting and cumulative clinical manifestations. Laboratory tests included the complete blood cell count, erythrocyte sedimentation rate, serum creatinine, cholesterol, urinalysis, urine protein to creatinine ratio, C3, C4, and anti-dsDNA.

These are done as requested per visit with some patients having limitation to do all tests due to financial constraints. The Systemic Lupus International

Collaborating Clinics/ACR Damage Index [18] is updated every 6 months. Treatment and the outcome of the condition were recorded.

Data was collected by means of an anonymous and confidential data sheet from the patients' files. The researchers first went through the patients' files to ensure that the patients included in the study sample were known SLE patients and collected the required demographic and disease information. A pilot study was conducted on the files of first five male SLE patients.

The data sheet was amended after the pilot study. Approval for the study was obtained from the Korle-Bu Teaching Hospital KBTH scientific and technical committee STC 00032/2018 for the study to be conducted. There was no need for informed consent as it was retrospective review of charts.

Statistical analysis

Data analysis was done using IBM SPSS Version 23. Continuous variables such as age, duration of illness and biochemical parameters were presented as means ± standard deviation. Categorical variables were presented as proportions. Statistical differences between the means and proportions were determined using the Student t-test, Chi square (x2) and Fisher's exact test where appropriate. A p value ≤ 0.05 was considered statistically significant.

RESULTS

There were 134 patients in the entire KBTH Lupus Cohort at the time of analysis. A total of 13 male patients with SLE in the KBTH Lupus Cohort were included in our analysis. They were all black Africans, mean age 30.62 ± SD8.47 yrs. with a range of 17 to 46 years. Most were Akans (50.0%) and had educational level up to tertiary level (75%) see Table 1.

All of them (100%) presented with constitutional features including fever, weight loss and night sweats. Cumulative ACR criteria included 61.5 % rash, 54.5 % oral ulcers, 92.3% arthritis, 61.5 % serositis, 38.5% renal involvement, 46.2 % CNS involvement and 15.4 % hematological.

Looking at their serological profile, 33.3 % had positive anti-dsDNA, 58.3 % Extractable nuclear antigens (ENA) mostly ribosomal antibodies in 58.3% and 91.7 % had a positive antinuclear antibody (ANA). See Table 2.

Table 3 shows the medications the participants were receiving. The mean duration of illness from onset of symptoms to diagnosis was 21.31 months years (range one to 100 months).

Male SLE patients had mean ESR value of 87.9 (p =0.001), CRP of 53.81(p= 0.041), Hemoglobin of 9.21g/dl (p=0.001) and an average weight of 68.58 (p=0.001). These data are presented in Table 4.

Table 1 Demographic Characteristics of Male SLE Patients

Demographic variables	**n (%)**
Ethnicity (N=12)	
Akan	6(50.0)
Ga/Adamgbe	2(16.7)
Ewe	3(25.0)
Northern tribe	1(8.3)
Place of birth (N=9)	
Northern Region	1(11.1)
Eastern Region	1(11.1)
Western Region	1(11.1)
Central Region	1(11.1)
Greater Accra Region	5(55.6)
Marital Status (N=13)	
Single	7(53.8)
Married	6(46.2)
Highest Educational Level (N=8)	
Basic	1
Secondary	1
Tertiary	6
Occupation (N=12)	
Professional/Technical/Related	3
Clerical work	1
Agricultural/Animal Husbandry	1
Pupil/Student	6
Unemployed	1

Table 2 Clinical Characteristics of Male SLE Patients complaints

	n (%)
General	13(100.0)
Cardiovascular System	4(30.8)
Central Nervous System	6(46.2)
Musculoskeletal System	12(92.3)
Dermatological	8 (61.5)
Gastrointestinal System	5(38.5)
Respiratory System	8(61.5)
Genito-urinary System	10(76.9)
Infections (Past or Present)	1(7.7)
Serology tests	
Antinuclear Antibodies	11(91.7)
Anti-double Stranded DNA	4(33.3)
Extractable Nuclear Antigens	7(58.3)
Ab to ENA – Smith	4(33.3)
Ab to ENA – Ro(SS-A)	4(33.3)
Ab to ENA – La(SS-B)	3(25.0)
Ab to ENA Ribosomal P	7(58.3)
SEROLOGY – Ab to ENA - RNP	5(41.7)

The average urine albumin creatinine ratio was 63.35 umol/l. Five patients were diagnosed with lupus

nephritis, all of them at time of diagnosis. There were no mortalities among the male SLE patients at the time of the study.

Table 3 Medication use among male SLE patients

Treatment	n (%)
Steroids (Oral/Injectable)	12(92.3)
Hematinic	2(15.4)
NSAIDs	6(46.2)
Proton Pump Inhibitors	10(76.9)
Azathioprine	3(23.1)
Hydroxychloroquine Use	11(84.6)
Mycophenolate	2(15.4)
Cyclophosphamide	3(23.1)
Statin	2(15.4)
ACE-Inhibitors	5(38.5)
Anticoagulation	1(7.7)

dsDNA: Double stranded deoxyribonucleic acid Ab: Antibodies ENA: Extractable nuclear antigen, ESR: Erythrocyte sedimentation rate SLE: Systemic lupus erythematosus

Table 4 Age and baseline laboratory variables of Male SLE patients in Ghana

Variables	Number	Mean (SD)
Age of patient (yrs.)	13	30.62 (8.47)
Erythrocyte sedimentation rate	10	87.90 (41.24)
C-Reactive Protein	10	53.81 (71.49)
Hemoglobin level	11	9.21 (1.95)
White Blood cell count	11	5.53 (2.68)
Platelet Count	11	266.45 (42.30)
URINEACR	7	63.35 (104.48)
complementc3	10	88.85 (37.95)
complementc4	10	21.93 (12.47)

ACR: albumin creatinine ratio

DISCUSSION

SLE is uncommon in males compared to females, especially during the childbearing years. [2] Because of the notion that SLE patients tend to be women, there may be a tendency to think about SLE as a possible diagnosis late in male patients presenting with symptoms that may not be typical like a rash or arthralgia and this can lead to a delay in diagnosis in men especially those who present with atypical symptoms.[2]

From this cohort, the ratio of male to female SLE cases was 1: 9.3. This compares with what Lu, Wallace et al. found which determined the incidence of SLE to be markedly increased in females of child-bearing age with a ratio of 8-15:1.[2] Font et al reported that out of the 261 patients with SLE, 30 were men (11.5%; female/male ratio 8.7:1).[19] This correlates with the findings of our study, where 10% were males. Similarly, Juan Liu et al also reported a female-to-male ratio of 8.14 to 1.[20] The mean age of male SLE patients in this cohort was 30.62 ± 8.47 years with a range of 17 to 46 years. demonstrating a younger age at diagnosis compared to the mean age of disease onset of 34 years (range14- 64) reported by Font et al [19].

Other studies have also showed an older population of patients at diagnosis with a mean age of 37.94±16.96 (range 10-87 years) and 35 ± 16.9years in another study.[20, 21]

The mean age was however older in our study compared to that done by Garcia MA et al where their cohort of male SLE patients were much younger with a median age at disease onset of 27 years and that at diagnosis of 29.2 years. (16) Males have been reported to experience their first SLE-related symptoms at a mean age range of 26 to 38.4 years in comparison with females who range from 26.3 to 31.9 years. The mean age range at diagnosis in males is reported to be between 26 to 55 years with females being diagnosed at a mean age of 27.9 to 42.6 years.[22, 23] Males therefore in other cohorts tend to be older both at diagnosis and at onset of disease symptoms. This may make diagnosis even more challenging as persons with SLE are typically assumed to be younger in the reproductive ages.

The mean duration of illness from onset of symptoms to diagnosis was 21.31 months, this is shorter compared to a study by Font et al where the mean duration of illness from onset of symptoms to diagnosis was 79 months.[19] Some studies report shorter duration of disease to diagnosis, but with evidence of disease causing damage to organs at the onset, which is reflected in higher early damage scores, Higher damage scores are associated with poor prognosis.[20] This suggests there may be more aggressive disease if males causing damage early despite their early diagnosis or males may under report symptoms that would have made diagnosis earlier.

Among African American population, median time from the first recorded criteria to diagnosis was significantly shorter in African-American (AA) males compared with AA females and also compared to European American (EA) females and males combined. African-American men progress from initial clinical manifestations to SLE diagnosis more rapidly than other ethnic or gender groups.[24] This would reflect what happens in our cohort as well, with rapid symptoms making diagnosis faster and earlier damage due to more aggressive disease.

Clinical features

The main clinical presentation of SLE in men in our cohort was arthritis, rash, oral ulcers and serositis which occurred at a higher frequency.

Constitutional symptoms of fever, weight loss and night sweats were elicited in all the patients. The most common symptom reported based on ACR criteria was arthritis

which 92.3% of our study population had. Our findings are comparable to a study done by Blažíčková and Rovenský where the most common symptom experienced was arthritis.[21]

A significant number of males had major organ involvement namely renal and CNS, with 5 patients (38.46%) diagnosed with lupus nephritis at the time of diagnosis and % having CNS involvement. This is consistent with other studies which recorded higher incidence of end organ damage in males. Nephritis is a common feature in studies looking at male SLE patients.[20, 25-28] Font et al found the incidence of nephropathy, neurological disease, thrombocytopenia, vasculitis, and serositis to be similar among males and females. [29] In study by Juan Liu et al 85.9% of males had renal involvement .[20]
This is higher than the findings of our study whereby five patients (38.5%) were diagnosed with lupus nephritis. Male SLE is associated with higher incidence of nephropathy, cardiovascular involvement, thrombotic phenomena and anti-ds-DNA antibodies which confer a higher mortality rate.[22]

Other studies report shorter delay to diagnosis, higher incidence of fever, weight loss, arterial hypertension, hemolytic anemia, IgG anticardiolipin antibodies and low complement among male SLE patients.[29] Another study done amongst Indian men with SLE showed that males have an earlier age of disease onset, a higher incidence of mucocutaneous and renal involvement and a lower incidence of neuropsychiatric, gastrointestinal and hematological disease in comparison to those published from the developed countries. A higher frequency of infection, particularly tuberculosis was seen which the cause of some deaths was.[30] Recent studies suggest organ impairment tend to occur in older men with SLE and they have higher mortality in one year suggesting men with lupus have a more complex clinical course.[23, 31] What drives this would be a focus of further studies.

Antibody profile and outcome
Antinuclear antibodies (ANA) (90.9%) were the most common serological marker identified. Anti-dsDNA which is thought to confer a higher mortality rate was found in about a third (33.3%) of the patients. Juan Liu et al found in the Chinese population, 47.1% of male SLE patients had a positive anti-dsDNA, and similar numbers as in our cohort (90.6%) had positive antinuclear antibody which compares with the findings of this study.[20] Most studies report a higher lupus anticoagulant positivity in male SLE patients[20], this was however not checked in our cohort as a routine.

Other studies have found no significant immunological differences between men and women.[19]

Mortality also is reported to be higher in men,[22, 25, 27] however, none of our male SLE patients died in contrast to reports of higher mortality from most studies and despite the more aggressive disease. This observation would need further follow up to determine if this remains so as this is a young cohort with a short follow-up period. The diagnosis of SLE should be considered in any patient with systemic symptoms including males, which would lead to less delay in diagnosis and management and help prevent irreversible damage to target organs.[31]

CONCLUSION

Male SLE patients in our inception cohort in Ghana show similar clinical features comparable to other populations, with arthritis and constitutional features as a predominant early feature, and Lupus nephritis being the main early indicator of damage. There were however no mortalities. This should warrant aggressive management in male patients as damage tends to occur early and there should also be a diligent watch for the development of lupus nephritis.

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